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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,877	06/28/1999	VIRGINIA M.-Y. LEE	PENN-0583	1398

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/06/2002 18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,877	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 08 August 2002 (Paper No. 16) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/297,877 is acceptable and a CPA has been established. An action on the CPA follows.

Status of Application, Amendments and/or Claims

The amendment of 08 August 2002 (Paper No. 17) has been entered in full. Claim 2 is cancelled and claim 4 is added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 4 is under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the specification at pg 2 of the previous Office Action (Paper No. 14, 08 February 2002) is *withdrawn* in view of the submitted abstract (Paper No. 17, 08 August 2002).

2. The rejection of claim 2 under 35 U.S.C. § 112, first paragraph (enablement and new matter) at pg 3-6 of the previous Office Action (Paper No. 14, 08 February 2002) are withdrawn in view of the cancelled claim (Paper No. 17, 08 August 2002).

Specification

3. The disclosure is objected to because of the following informalities:

3a. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "ADMISTRATION OF AN AGENT WHICH DECREASES PROCESSING OF AMYLOID PRECURSOR PROTEIN".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, claim 4 recites a method of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brains of patients with Alzheimer's disease comprising administering to a patient an agent which decreases processing of amyloid precursor protein into amyloid β peptides wherein said agent is identified by (i) contacting NTN2 cells the agent and (ii) measuring levels of amyloid β peptides formed in the endoplasmic reticulum (ER) of the cells.

The specification teaches that NT2N neurons are metabolically labeled with [^{35}S]methionine in the presence or absence of Brefeldin A (BFA) (pg 9, lines 2-4). The specification discloses that in the absence of BFA, full length APP, APPβ, and Aβ are recovered from cell lysates while APPα, APPβ, and Aβ are detected in the media of the NT2N neurons. The specification also teaches that in the presence of BFA, full length APP, APPβ, and Aβ are recovered from NT2N cell lysates, but the secretion of APPα, APPβ, and Aβ into the medium is completely abolished in the presence of BFA (pg 9, lines 8-13). Furthermore, the specification teaches that an ER-retention signal is placed in APP695 ($APP695_{\Delta KK}$) wherein this lysine motif signal is sufficient to retain heterologous transmembrane proteins in the ER and intermediate

compartment (pg 9, lines 33-37). BFA treatment of NT2N neurons expressing $APP695_{\Delta KK}$, blocks surface expression of APP695 while $APP695_{\Delta KK}$ does not acquire resistance to endoglycosidase H digestion, indicating that $APP695_{\Delta KK}$ is retained in the ER (pg 10, lines 13-18). The specification also discloses that SFV-infected NT2N cells are metabolically labeled overnight and Aβ is immunoprecipitated from the medium and cell lysate. The specification teaches that ER retention of APP by the KK retention signal blocks Aβ secretion, but fails to block all intracellular Aβ biosynthesis. The specification teaches that as with Brefeldin A (BFA) treatment, cells expressing $APP695_{\Delta KK}$ produce 40% of the total intracellular Aβ generated from APP695. This reduction is because of the loss of Aβ40. Aβ42 levels are not effected (pg 10, lines 22-33).

However, the specification of the instant application does not teach any methods or working examples wherein a patient is administered an agent which decreases processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in brains of patients with Alzheimer's disease. Since there is inadequate guidance in the specification, the skilled artisan must use the current invention as a starting point for further experimentation. Furthermore, the present invention is unpredictable and complex wherein the claimed method may not necessarily inhibit the processing of amyloid precursor protein into amyloid β plaques *in vivo*. The skilled artisan must resort to trial and error experimentation to determine the optimal dosage, duration, and mode of administration of all possible agents. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

Additionally, since the specification provides no guidance regarding what sort of agents should be screened for inhibiting the processing of amyloid precursor protein, the skilled artisan must resort to trial and error experimentation to determine which class of compounds might yield one with the desired activity. Such trial and error experimentation is considered undue.

Furthermore, Alzheimer's disease is recalcitrant to treatment and relevant literature reports that there is no cure for Alzheimer's disease and that only recently have therapeutic *strategies* emerged (Brinton et al. Pharmaceutical Res 15(3): 386-398, 1998; pg 386, ¶ 1). For example, Brinton et al. indicates cholinergic pharmaceuticals only modestly improve cognitive function, have short-lived effects, and are in the early stage of development (Brinton et al., pg 393, col 2, ¶ 4 through pg 394). Brinton et al. also mentions that unlike animal studies with NGF, human trials have not been successful (pg 394, col 1). Additionally, Roses (Lancet 355: 1358-1361, 2000) discloses that "if an effective treatment were to be developed for a common form of the illness, it might not work for all patients, especially those with rare mutational forms of Alzheimer's disease. Conversely, a treatment developed for a specific mutation may have no effect in common Alzheimer's phenotypes" (pg 1358, bottom of col 1 through top of col 2). Roses also states that a patient's response to a drug may depend on other factors than the alleles the individual carries, such as drug distribution, drug absorption, drug concentration at the target site, and drug metabolism and elimination (pg 1358, col 2, ¶ 1).

Due to the large quantity of experimentation necessary to identify an agent that decreases processing of amyloid precursor protein and to determine the optimal dosage, duration, and mode of administration of all possible agents to a patient, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to

the same, the complex nature of the invention, the contradictory state of the prior art, and the unpredictability of the effects of inhibiting the processing of amyloid precursor protein into amyloid β plaques *in vivo*, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. admits

Conclusion

Claim 4 is not allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Cook et al. Nature Medicine 3(9) : 1021-1023, 1997

Huse et al. Mol Neurobiol 22(1-3):81-98, 2000

Gandy et al. U.S. Patent 5,242,932

Buxbaum et al. U.S. Patent 5,538,983

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kunnen

BEB
Art Unit 1647
October 30, 2002